

EXHIBIT 7

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January 23, 2007

Re: Talia Hinman
Policy holder: Melinda Hinman
Reference #: 052563800

Dear Doctor:

Ms. Hinman is appealing to you because you have concluded that the treatment Ms. Hinman received was experimental and investigational and refused her reimbursement. In fact the treatment followed standard of care. Please see attached a letter prepared by Dr. Deborah Metzger with citations and the article by Johnston and Stricker: Treatment of Lyme Disease a Medicolegal assessment. These provide ample citations to support treatment.

Ms. Hinman had Lyme disease with Arthritis, Encephalopathy and Neuropathy, which did not resolve with oral antibiotic treatment. Ms. Hinman responded well but not completely to oral medications. She was placed on intravenous and is now well and able to return to work and school, work and her previously active life.

Lyme disease is not diagnosed by laboratory testing as both the CDC and NIAID have concluded that the testing is currently not sensitive or specific enough for diagnosis. The advice to the physician is to diagnose the patient on clinical grounds and use testing to confirm exposure to the spirochete pathogen. The Lyme patient presents with an extremely characteristic group of symptoms. However as noted below from the Evidence based guidelines for the management of Lyme disease (guidelines.gov). Talia Hinman has multisystemic signs and symptoms that are diagnostic of Lyme disease.

Ms. Hinman presented to our clinic as a 17-year-old athlete. In December 2002 while snowboarding she became fatigued and had to go sit into the lodge and rest, which was extremely uncharacteristic for her. She thought she had the flu, as her throat was sore, she had vertigo and felt nauseas. The symptoms did not resolve in the usual time for a virus; rather the symptoms persisted for several weeks. Between January and March of 2004 she developed a hip injury diagnosed as a bursitis since x-rays were normal. She had trouble pitching (her usual position) and had to rest and avoid participating in the sport for periods of time.

In March 2003 she attempted to return to her team to see if the hip had recovered sufficiently to let her pitch. The "flu" came back at beginning of March and she could not get rid of it. So at softball practice she would get flushed, sick, and nauseas and be unable to play. She developed more symptoms including headache, bouts nausea and back pain.

She tried to continue to play softball as she was a key player on her team and she loved to play. She lost 20 pounds between mid March and May without intention, probably secondary to the nausea. She developed migraines. The migraines became daily and she became bed ridden. She had sweats and nocturnal diaphoresis. Balance became much more difficult and she frequently felt dizzy and dystaxic. Her ankles began to swell.

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The head pain felt like her eyeballs were being squeezed from inside. When this pain occurs she needs to lay down in the dark. Phono and photophobia developed. Imitrex helps intermittently but not consistently. Headaches became daily and incapacitating. The patient developed ear pain and tinnitus.

The patient developed cognitive problems. She found focusing hard. Sometimes she could not figure out what a math page was about and she has been consistently in the Gifted and Talented program and math has been a favorite subject. She used to read a lot and found in July 2004 that she could not even read a label of a can.

In addition to the above symptoms Ms. Hinman developed shooting pains in her hips, neck and lower back. She had played sports for years and understood the stress on the body of working out. However these symptoms did not feel like her usual work out fatigue or tension. They were more intense and had the description of shooting pains rather than the familiar muscle aching after a hard ball game. Ms. Hinman also developed an extremely stiff neck for the first time, in spite of no change in her work outs, no accidents and no apparent neck trauma. Her low back and hips hurt severely at times so she could not walk. At end of the softball season in March 2003, Ms. Hinman played no sports for 6 months because her parents insisted, thinking that the rest would help her recover. So July 2003-March 2004 she relaxed, played no fall sport, no soccer with the intention of being able to be ready in Spring 2004 for her favorite sport, softball.

When she returned to softball in March 2004, her hips and back hurt at times intensively. She was highly motivated and played through the pain in her hip. She developed back pain. Through April 2004 symptoms intensified and she had severe incapacitating pain in her neck, back and hip.

Gastrointestinal symptoms developed in March 2004 including constipation alternating with diarrhea and nausea and vomiting

The patient developed non restorative sleep. At times she would sleep 12 hours and still be unable to get up due to fatigue for the rest of the day. In the past Ms Hinman had never needed much sleep and her mother noted that Talia was a teenager who arose and organized herself in the morning without need of a call or a push. After her illness started, sleeping pattern became non restorative and erratic.

Ms. Hinman developed multisystemic disease, which involved meningeal, central nervous system, joint, peripheral nervous system and gastrointestinal symptoms.

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From Evidence based guideline in the management of Lyme Disease :
"Treatment decisions should not be based routinely or exclusively on laboratory findings. The two-tier diagnostic criteria, requiring both a positive enzyme-linked immunosorbent assay (ELISA) and western blot, lacks sensitivity and leaves a significant number of individuals with Lyme disease undiagnosed and untreated. These diagnostic criteria were intended to improve the specificity of tests to aid in identifying well-defined Lyme disease cases for research studies. Though arbitrarily chosen, these criteria have been used as rigid diagnostic benchmarks that have prevented individuals with Lyme disease from obtaining treatment. Diagnosis of Lyme disease by two-tier confirmation fails to detect up to 90% of cases and does not distinguish between acute, chronic, or resolved infection.

Ms. Hinman's laboratory testing was positive for Lyme exposure and revealed a positive IgM and IgG Western blot to *Borrelia burgdorferi*. Patient had the 31kda Osp A band as well as the 39kda band. Epstein Barr panel suggested past infection, which revealed a conversion from earlier studies. Most likely this patient had mononucleosis and was infected with *Borrelia burgdorferi*. I have had several cases of acute mononucleosis with acute Lyme disease in my practice and these patients have prolonged courses of Lyme disease. CD57 Natural Killer cell subset was remarkably low. WA-1 Babesia antibody was positive at 1:640.

ANA, RF and sedimentation rate were unremarkable. Cat scan of the sinuses was unremarkable. Abdominal cat scan was normal.

From Evidence based guidelines for the Management of Lyme disease:
"Treatment decisions should not be based routinely or exclusively on laboratory findings. The two-tier diagnostic criteria, requiring both a positive enzyme-linked immunosorbent assay (ELISA) and western blot, lacks sensitivity and leaves a significant number of individuals with Lyme disease undiagnosed and untreated. These diagnostic criteria were intended to improve the specificity of tests to aid in identifying well-defined Lyme disease cases for research studies. Though arbitrarily chosen, these criteria have been used as rigid diagnostic benchmarks that have prevented individuals with Lyme disease from obtaining treatment. Diagnosis of Lyme disease by two-tier confirmation fails to detect up to 90% of cases and does not distinguish between acute, chronic, or resolved infection.

Persistent Lyme Disease

Persistent Lyme disease is more resistant to treatment and more likely to produce a relapse. Although persistent Lyme disease may resolve without additional therapy, many experts believe that this condition should be treated with repeated and prolonged antibiotics. Physicians should extend the duration of antibiotics to prevent or delay recurrent and refractory Lyme disease."

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Talia Hinman had good but incomplete response to oral antibiotics for Lyme disease. She was able to graduate with her class although it was difficult overall for her to achieve that goal; she is a resilient and determined young woman and pushed herself through. Ms. Hinman noted that after oral antibiotics most vertiginous episodes resolved, nausea became rare and her fatigue significantly improved. Low fevers, nocturnal diaphoresis and rashes resolved. She could exercise carefully, not to her previous athletic level but she could start working out in a gym. However she continued to have joint pain in her neck, low back and hips. She also has neuropathic symptoms in her hip, neck and low back. Headaches have decreased but not resolved. Meningeal symptoms including photophobia and phonophobia continued to a lesser degree.

Rocephin, 2grams daily for 60 days for 3rd stage Rheumatologic and Neurologic Lyme unresponsive to oral treatment. Rocephin was continued as directed by the Standard of care in Evidence based guidelines for the treatment of Lyme disease, until symptoms had resolved. The patient is fully recovered and has returned to full time work and schooling.

Sincerely:

Christine Green MD

Att Letter by Dr. Metzger, please see appendices A and B
Article

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Lyme Disease Medical Policy

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FILE COPY**Lyme Disease****Medical Policy #185A****Clinical Decision Making****Alternate names**

- Lyme-like disease
- Chronic Lyme disease
- Post-Lyme disease syndrome
- Post Lyme syndrome, PLS
- LD
- Lyme arthritis

Related terms

Lyme carditis, Annular lesions, Tick-borne disease, Erythema chronicum migrans (ECM), Erythema Migrans, Ixodes, Borrelia burgdorferi, Polymerase chain reaction (PCR), IgM, IgG, Parenteral antibiotics, Spirochetal infection, Ceftriaxone, Cefotaxime, Doxycycline, Amoxicillin

Background/Summary

Lyme disease (LD) is a multi-system disease caused by the spirochete bacterium, *Borrelia burgdorferi*. These bacteria are transmitted to humans by the bite of infected ticks (usually *Ixodes* sp.) Both deer and rodent hosts are necessary to maintain the enzootic cycle of *B.burgdorferi*. The *I. scapularis* tick may also transmit *Anaplasma phagocytophilia*, which causes human granulocytic ehrlichiosis (HE), and babesiosis, which is caused by a red blood cell protozoan. Lyme disease is the most common vectorborne disease in the United States. Over ninety percent of cases come from Connecticut, Rhode Island, New York, Pennsylvania, Delaware, New Jersey, Maryland, Massachusetts, and Wisconsin. Its clinical hallmark is an early expanding skin lesion, erythema chronicum migrans (ECM), which can be followed months to years later by neurologic, cardiac or joint abnormalities. All stages of Lyme disease respond to antibiotics but early stage treatment has the most favorable results. Some providers believe that vague constitutional symptoms and fatigue are caused by lingering infection with the Lyme spirochete. Long-term antibiotic treatment for chronic symptoms is not supported by the medical literature.

Signs and symptoms of Lyme disease

The infection is grouped into three distinct stages based on clinical presentation and length of time since the acute exposure. These stages may overlap and most patients do not exhibit all:

Stage 1 (primary Lyme disease): Localized infection

- Erythema migrans in 60 - 80% of people
- Malaise
- Fever
- Headache
- Myalgias
- Arthralgias
- Some patients have no symptoms

Stage 2 (secondary Lyme): Disseminated infection - days to weeks after untreated primary Lyme disease

- Multiple erythema migrans lesions
- Bell's palsy, or other facial nerve problems
- Meningitis
- Encephalitis
- Heart block
- Pericarditis, myocarditis
- Orchitis
- Hepatitis
- Iritis

Stage 3 (tertiary Lyme): Late/persistent infection - months to years after untreated primary Lyme disease

- Recurrent synovitis
- Recurrent tendonitis and bursitis
- Central nervous system symptoms: behavioral abnormalities, memory loss, dementia, depression, sleep disorders)
- Peripheral neuropathies

The later stages of Lyme disease may mimic other disorders like rheumatic fever, systemic infection (i.e., gonococcemia), Bell's palsy, multiple sclerosis, Guillain-Barre syndrome, primary psychosis, Reiter's syndrome and rheumatoid arthritis. Late stage disease can result from early disease that was unrecognized or failed to respond to treatment, or from asymptomatic infection. Late stage disease may require more intensive therapy and can result in permanent sequelae even if treated adequately.

Table 1: signs and symptoms of late stage Lyme disease

Neurologic involvement

Encephalitis, encephalopathy
 Aseptic, lymphocytic meningitis
 Meningoencephalitis
 Cranial neuritis
 Mononeuritis multiplex.
 Acute painful radiculoneuritis (Bannwarth's syndrome, Lymphocytic meningoradiculitis)
 Encephalopathy—(manifested primarily by subtle cognitive disturbances)
 Chronic axonal polyradiculoneuropathy, radiculopathy
 Chronic encephalomyelitis
 Late neuroborreliosis affecting the CNS or peripheral nervous system

Cardiac involvement

Carditis
 Conduction system disease—atrioventricular block (first degree, Wenkebach, or complex heart block)
 Mild left ventricular dysfunction
 Cardiomegaly

Diagnosis

Diagnosis is based on clinical manifestations, epidemiologic information and laboratory evaluation. Diagnosis in the United States is based on:

1. clinical findings consistent with the disease
2. a history of exposure in an endemic area
3. except for those patients with erythema migrans, a positive ELISA and Western Blot

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Serologic support for the diagnosis of Lyme disease may also be problematic early in the infection. The CDC recommends testing initially with an enzyme-linked immunosorbent assay (ELISA) or an indirect fluorescent antibody (IFA) test, followed by testing with immunoblot (Western immunoblot WB) test to corroborate ambiguous or positive results obtained with the first test. Asymptomatic individuals in endemic areas will have positive serology but no clinical manifestation of Lyme disease. Treatment is not indicated without the appropriate clinical findings. Tests such as the Lyme urine antigen test, which has given grossly unreliable results, should not be used to support the diagnosis of Lyme disease. There is insufficient evidence to support the use of the urine antigen assay in clinical practice. The detection of Lyme antigen by polymerase chain reaction or PCR in blood, urine, synovial fluid, or CSF has not been standardized for routine diagnosis of Lyme disease. (source; CDC). This technique is still considered investigational and is properly classified as a research tool.

Note to reviewers

Western Blot assays are not useful in the diagnosis of early acute Lyme infection. Only half of EM cases are seropositive (Coyle 2002). At around 2 weeks after inoculation, when EM rash is visible, IgM reaction may be the only Western blot reactivity detected. Testing is not always performed in this instance as the history and rash are diagnostic. A few weeks after the acute exposure, IgG bands develop and can coexist with stable or declining IgM reactivity. With resolution of symptoms, IgG reactivity continues, but can decrease or resolve with treatment. Patients with late Lyme disease may remain seropositive for many years after successful treatment.

Treatment

Overview: Antibiotic treatment for 10 days with an oral antibiotic is usually effective early in the disease. Patients with the later disease form and those refractory to oral antibiotic treatment, may require treatment with intravenous antibiotic. Parenteral antibiotics given for a 28 day course are recommended for treating cardiac and neurological manifestations. Persistent or recurrent symptoms after appropriate antibiotic therapy often can be attributed to causes other than persistent infection.

"Chronic Lyme disease" and "Post-Lyme disease syndrome"

After appropriately treated Lyme disease, a small percentage of patients continue to have subjective symptoms — musculoskeletal pain, neurocognitive difficulties, or fatigue — that may last for years. This potentially disabling syndrome is sometimes called "chronic Lyme disease" or "post-Lyme disease syndrome," and is similar to chronic fatigue syndrome or fibromyalgia. This nomenclature refers to a cluster of diffuse symptoms. There is currently no convincing evidence that the syndrome is caused by active or untreated infection. Nonspecific symptoms in individuals with positive serology should not be treated with prolonged antibiotic therapy.

Some providers believe that long-term intravenous antibiotics can ameliorate the symptoms of "chronic Lyme disease". However, In a study of patients with post-Lyme disease syndrome who received either intravenous ceftriaxone for 28 days followed by oral doxycycline for 60 days or intravenous and oral placebo preparations for the same duration, there were no significant differences between the groups in the percentage of patients who said that their symptoms had improved, gotten worse, or stayed the same. (Klempner MS, et al. NEJM 2001 ;345:85-92)

Such patients are best treated symptomatically rather than with prolonged courses of antibiotic therapy. Prolonged ceftriaxone therapy for unsubstantiated Lyme disease has resulted in biliary complications; and in one reported case, the prolonged administration of cefotaxime resulted in death. (Medical Progress: Lyme Disease. Steere A. C New England Journal of Medicine Vol.345:115-125 July 2001 No 2).

The Infectious Disease Society of America (IDSA) recently published guidelines for treatment of different stages of Lyme disease. The practice guidelines indicate that Ceftriaxone (2 g iv daily) although effective, is not superior to oral agents and is not recommended as a first-line agent for treatment of Lyme disease. Intravenous antibiotics are recommended for neurologic infection, (except in isolated facial nerve palsy) and in severe cardiac abnormalities. Regarding "chronic Lyme disease or post-Lyme disease" the IDSA cites:

"Randomized controlled studies of treatment of patients who remain unwell after standard courses of antibiotic therapy for Lyme disease are in progress. To date, there are no convincing published data that repeated or

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prolonged courses of either oral or iv antimicrobial therapy are effective for such patients. The consensus of the Infectious Diseases Society of America (IDSA) expert-panel members is that there is insufficient evidence to regard "chronic Lyme disease" as a separate diagnostic entity."

Patient does not have diagnostic confirmation of Lyme disease.

(A) Conclusion - RN
Experimental/investigational.

Rationale

The patient does not meet one or more of the diagnostic criteria for Lyme Disease. The treatment of Lyme disease in the absence of a confirmed diagnosis is experimental/investigational.

Diagnosis is based on clinical manifestations, epidemiologic information and laboratory evaluation. Diagnosis in the United States requires:

1. clinical findings consistent with the disease; and
2. a history of exposure in an endemic area; and
3. either
 - a. the presence of erythema migrans, OR
 - b. a positive ELISA and Western Blot

IV antibiotic use: Patient does not have neurological or severe cardiac symptoms OR patient does not have history of failed oral antibiotic therapy.

(B) Conclusion - MD
Experimental/investigational.

Rationale

Intravenous antibiotic therapy initiated prior to standard oral antibiotic therapies is experimental/investigational for the treatment of Lyme disease. There are no statistically valid, well-designed, randomized controlled trials supporting Intravenous antibiotic therapy in patients who do not have neurological or cardiac symptoms OR have not failed oral antibiotic therapy.

IV antibiotics used beyond 28 days

(C) Conclusion - RN
Experimental/investigational.

Rationale

There are inadequate, published, peer-reviewed, well-designed, statistically valid studies documenting additional efficacy of IV antibiotic therapy for Lyme disease beyond 28 days. Repeated or prolonged courses of either oral or IV antimicrobial therapy are not effective for patients who remain unwell after standard courses of antibiotic therapy for Lyme disease.

IV antibiotic therapy for 28 days or less.

(D) Conclusion - MD
Medically necessary.

Rationale

The treatment is medically appropriate. There are sufficient published, peer-reviewed studies documenting the efficacy of IV therapy for late stage Lyme disease. The treatment duration does not exceed 28 days.

Oral antibiotic regimen for greater than 28 days.

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(E) Conclusion - RN
Experimental/Investigational.**Rationale**

Treatment with oral antibiotic regimen for greater than 28 days is not supported by well-designed peer-reviewed, statistically valid medical studies.

Oral antibiotic regimen for 28 days or less.**(F) Conclusion - RN**
Medically necessary.**Rationale**

The treatment is medically appropriate.

Appendix 1:**Lyme disease diagnostic criteria**

A positive IgM or a positive IgG immunoblot confirms the diagnosis of Lyme disease. **CDC criteria for a positive Western Blot:**

**It is recommended that an IgM immunoblot be considered positive if 2 of the following 3 bands are present:

IgM immunoblot - Two of the following three bands are present:

- 24/21*, 23** (OspC)
- 39 kDa (BmpA)
- 41 kDa (Fla)

*The apparent molecular mass of OspC is dependent on the strain of *B. burgdorferi* being tested. The 24 kDa and 21 kDa proteins referred to are the same.

Source: *Notice to Readers Recommendations for Test Performance and Interpretation from the Second National Conference on Serologic Diagnosis of Lyme Disease* CDC MMWR 44(31);590-591 08/11/1995

**Meyerhoff J. Johns Hopkins 10/2004 Lyme Disease
 Rothermel H, et al. Pediatrics Aug 2001 Optic Neuropathy in children with Lyme Disease
 University Utah ARUP labs 2004 http://www.aruplab.com/guides/clt/tests/clt_a110.jsp accessed 10/6/04
 Reed KD Marshfield Clinic Laboratory Testing for Lyme Disease Feb 2002
 Steere AC. Lyme Disease NEJM 345 no. 2 July, 2001

**It is recommended that the IgG immunoblot be considered positive if 5 of the following 10 bands are present:

- 18 kDa
- 21 kDa (OspC)
- 28 kDa
- 30 kDa
- 39 kDa (BmpA)
- 41 kDa (Fla)
- 45 kDa
- 58 kDa (not GroEL)
- 66 kDa
- 93 kDa

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(When Western immunoblot is used during the first 4 weeks of disease onset (early LD) both IgM AND IgG procedures should be performed.)

Source: CDC Notice to reader's recommendations for test performance and interpretation from the second national conference on serologic diagnosis of Lyme disease. Aug. 11, 1995 44(31);590-591

Appendix 2:

Treatment Recommendations, Infectious Disease Society of America

IDSA recommendations

Indication	Treatment	Duration, d
Tick bite	None recommended; observe	
E. Ixodes scutigerus	Oral regimen ^{a,b}	14-21
Acute neurological disease		
Meningitis or radiculopathy	Parenteral regimen ^c	14-28
Cranial-nerve palsy	Oral regimen ^d	14-21
Cardiac disease		
1st or 2d degree heart block	Oral regimen ^a	14-21
3d degree heart block	Parenteral regimen ^{b,d}	14-21
Late disease		
Arthritis without neurological disease	Oral regimen ^e	28
Recurrent arthritis after oral regimen	Oral regimen ^e or parenteral regimen ^f	28
Persistent arthritis after 2 courses of antibiotics		
CNS or peripheral nervous system disease	Symptomatic therapy	14-28
Chronic Lyme disease or post-Lyme disease syndrome	Parenteral regimen ^g	14-28
	Symptomatic therapy ^g	

^a See table 2.

^b For adult patients who are intolerant of amoxicillin, doxycycline, and cefuroxime axetil, alternatives are aztreonam (300 mg orally daily for 7-10 days), cefixime (300 mg orally 4 times per day for 14-21 days), or clarithromycin (300 mg orally twice daily for 14-21 days [except during pregnancy]). The recommended dosages of these agents for children are as follows: aztreonam, 10 mg/kg daily (maximum, 500 mg/d); cefixime, 12.5 mg/kg, 4 times daily (maximum, 500 mg/d); clarithromycin, 7.5 mg/kg twice daily (maximum, 500 mg/d). Patients treated with macrolides should be closely followed.

^c For nonpregnant adult patients intolerant of both penicillin and cephalosporin, doxycycline (200-400 mg/d orally [or iv if oral medications cannot be taken], divided into 2 doses) may be adequate.

^d A temporary pacemaker may be required.^e See the discussion of Chronic Lyme Disease or Post-Lyme Disease Syndrome in the text.

Source: Clinical Infectious Diseases 2000;31(Suppl 1):S1-14.

Appendix 3:

Lyme Disease vaccine: LYMErix

GlaxoSmithKline, the maker of the only Lyme disease vaccine, pulled LYMErix off the market in February 2002, citing poor sales. Lymerix had caused controversy in recent years, with numerous filed lawsuits against maker claiming the vaccine made patients sick. The Food and Drug Administration had found no proof that the vaccine was dangerous and did not order the manufacturer to end sales.

Note to reviewers:

Lyme disease tests whose accuracy and clinical usefulness have not been established.

- Urine antigen test
- Immunofluorescent staining for cell wall-deficient forms of *Borrelia burgdorferi*
- Lymphocyte transformation tests

In addition, some labs perform polymerase chain reaction tests for *B. burgdorferi* DNA on inappropriate specimens such as blood and urine or interpret Western blots using criteria that have not been validated and published in peer-reviewed scientific literature.

Source: Caution Regarding Testing for Lyme Disease JAMA April 20, 2005 Vol.293 No.15 pg. 1853

Medical Literature Review

CDC Recommendations for the use of lyme disease vaccine recommendations of the advisory committee on immunization practices (ACIP) June 4 1999/ 48(RR07);1-17. available on the www at <http://www.cdc.gov/mmwr/PDF/RR/RR4807.pdf> [Accessed 7/12/2005]

CDC Notice to readers recommendations for test performance and interpretation from the second national conference on serologic diagnosis of Lyme disease. Aug. 11, 1995 44(31);590-591.

Summary of criteria for Western Blot interpretation in the diagnostic evaluation of Lyme disease.

Coyle PK, Schutzer SE. Neurologic Aspects of Lyme Disease. Tick-Borne Diseases. Medical Clinics of North America Vol 86 no.2 March 2002

This is a review of 85 studies, topics included are epidemiology, vectors and hosts, clinical disease with staging, neurological involvement and treatment.

Fleming RV, et al. Pre-treatment and post-treatment assessment of the C(6) test in patients with persistent symptoms and a history of Lyme borreliosis Eur J Clin Microbiol Infect Dis. 2004;23(8):615-618.

This study evaluated the C(6) test as a predictor of therapy outcome in a population of patients with post-treatment Lyme disease syndrome. The serum specimens tested were from patients with well-documented, previously treated Lyme borreliosis who had persistent musculoskeletal or neurocognitive symptoms. All of the patients had participated in a recent double-blind, placebo-controlled antibiotic trial in which serum samples were collected at baseline and 6 months thereafter 3 months following treatment termination. In this patient population no correlation was found between a decline of C(6) antibody titer of any magnitude and treatment or clinical outcome. Antibodies to C(6) persisted in these patients with post-treatment Lyme disease syndrome following treatment, albeit at a markedly lower prevalence and titer than in untreated patients with acute disseminated Lyme disease. The results indicate that C(6) antibody cannot be used to assess treatment outcome or the presence of active infection in this population.

Hayes Technology Assessment Lyme Disease, Laboratory Diagnosis July 2003 Hayes Update Search 8/2004

Efficacy remains unchanged from 2003 Directory Report.

No anticipated impact on HAYES Ratings.

Serological Testing:

B – For two-test protocol using an enzyme-linked immunosorbent assay (ELISA), immunofluorescent assay (IFA), or immunochromatographic assay as initial test and immunoblot as confirmatory test for diagnosis of LD.

B – For protein-specific ELISA as an initial test and immunoblot as confirmatory test for diagnosis of LD.

B – For Western immunoblot as confirmatory test for diagnosis of LD.

C – For hemagglutination assay (HA), IHA, borrellicidal antibody assay (BAT), immune complex enzyme immunoassay (EIA), or immune complex EIA (EMIBA) as initial test and immunoblot as confirmatory test for diagnosis of LD.

D – For any first-tier serological test performed alone as an initial test. This Rating reflects evidence that first-tier serological tests are relatively nonspecific, and therefore cannot be used alone for definitive diagnosis of LD.

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PCR-based Analysis:

- C – For PCR-based analysis for diagnosis of early LD with atypical presentation, or weak history of exposure in LD-endemic area.
- C – For PCR-based analysis for diagnosis of late stage LD.
- D – For PCR-based analysis for diagnosis of early localized LD.
- D – For PCR-based analysis for diagnosis of early disseminated LD.

The D Ratings reflect the lack of evidence that PCR-based analysis is sufficiently accurate to support a definitive diagnosis in patients with early stage LD.

Culture:

- D – For biopsy culture for diagnosis of any stage of LD. This Rating reflects the lack of evidence regarding the sensitivity and specificity of this testing method for diagnosis of LD.

Hengge U, Tannapfel A, et. al., Lyme borreliosis, *The Lancet Infectious Diseases*, Volume 3, Number 8, August 2003.

This is a review article published by German authors. The stated purpose of the article is to "present evidence-based treatment recommendations for Lyme borreliosis and review the prevention of Lyme borreliosis, including the Lyme vaccine." The authors review the Epidemiology, causative organisms, immune responses and clinical manifestations of the condition including regional variations attributed to different *Borrelia* subtypes seen in Europe and America. Because of the unreliability of antibody tests and culture difficulties in extracutaneous Lyme borreliosis, the authors document a two-step serologic approach to diagnosis. "A positive or equivocal first test, usually an ELISA or indirect immunofluorescence assay (IFA), is followed by an immunoblot test on the same serum sample, which can detect IgM and IgG antibodies to individual *B burgdorferi* antigens; in general, two independent bands are needed for a positive immunoblot test result. If the western blot is negative, the reactive ELISA or IFA very probably was a false positive result. Neither ELISA nor immunoblot permits detection of fourfold rises in antibody (seroconversion). Since IgM and IgG antibodies to *B burgdorferi* in serum may persist for years after clinical recovery, serology is insufficient to measure the response to treatment."

Treatment recommendations: "Evidence-based treatment recommendations for Lyme borreliosis have been proposed by the Infectious Disease Society of America and The American College of Physicians." For early localized and disseminated infection, treatment with doxycycline for 14-21 days is recommended in people older than 8 years of age, except for pregnant women. "A most recent phase II study on the duration of doxycycline treatment revealed no benefit of a 20-day regimen compared with only ten days of treatment." "For patients with objective evidence of neurologic abnormalities, 1 2-4 week course of intravenous ceftriaxone is most commonly administered."

"After appropriate treatment of Lyme borreliosis, a small percentage of patients continued to have subjective symptoms, primarily musculoskeletal pain, neurocognitive difficulties, or fatigue that may last for years. This disabling syndrome is sometimes called 'chronic Lyme borreliosis' or post Lyme borreliosis syndrome'; it has similarities with chronic fatigue syndrome or fibromyalgia. This post-infectious syndrome occurs more frequently in patients whose symptoms are suggestive of early dissemination of the spirochete to the nervous system, particularly when treatment is delayed. Such patients are best treated symptomatically rather than with prolonged courses of antibiotic therapy."

Kaplan RF, Trevino RP, Johnson GM, Levy L, Dornbush R, Hu LT, Evans J, Weinstein A, Schmid CH, Klempner MS. Cognitive function in post-treatment Lyme disease Do additional antibiotics help? *Neurology*. 2003 Jun 24;60(12):1916-22

The objective of this study was to determine whether antibiotic therapy improves cognitive function in two randomized double-blind placebo-controlled studies of patients with post-treatment chronic Lyme disease (PTCLD). 129 patients with a physician-documented history of Lyme disease from

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three study sites in the northeast United States were studied. Seventy-eight were seropositive for IgG antibodies against *Borrelia burgdorferi*, and 51 were seronegative. Patients in each group were randomly assigned to receive IV ceftriaxone 2 g daily for 28 days followed by oral doxycycline 200 mg daily for 60 days or matching IV and oral placebos. Assessments were made at 90 and 180 days after treatment. Symptom severity was measured from the cognitive functioning, pain, and role functioning scales of the Medical Outcomes Study (MOS). Memory, attention, and executive functioning were assessed using objective tests. Mood was assessed using the Beck Depression Inventory and Minnesota Multiphasic Personality Inventory. Results showed there were no significant baseline differences between seropositive and seronegative groups. Both groups reported a high frequency of MOS symptoms, depression, and somatic complaints but had normal baseline neuropsychological test scores. The combined groups showed significant decreases in MOS symptoms, higher objective test scores, and improved mood between baseline and 90 days. However, there were no significant differences between those receiving antibiotics and placebo. The study concluded that patients with post-treatment chronic Lyme disease who have symptoms but show no evidence of persisting *Borrelia* infection do not show objective evidence of cognitive impairment. Additional antibiotic therapy was not more beneficial than administering placebo.

Klempner MS, Hu LT, Evans J, Schmid CH, Johnson GM, Trevino RP, Norton D, Levy L, Wall D, McCall J, Kosinski M, Weinstein A. Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. *N Engl J Med*. 2001 Jul 12;345(2):85-92.

Abstract:

It is controversial whether prolonged antibiotic treatment is effective for patients in whom symptoms persist after the recommended antibiotic treatment for acute Lyme disease. **METHODS:** We conducted two randomized trials: one in 78 patients who were seropositive for IgG antibodies to *Borrelia burgdorferi* at the time of enrollment and the other in 51 patients who were seronegative. The patients received either intravenous ceftriaxone, 2 g daily for 28 days, followed by oral doxycycline, 200 mg daily for 60 days, or matching intravenous and oral placebos. Each patient had well-documented, previously treated Lyme disease but had persistent musculoskeletal pain, neurocognitive symptoms, or dysesthesia, often associated with fatigue. The primary outcome measures were improvement on the physical- and mental-health-component summary scales of the Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36)—a scale measuring the health-related quality of life—on day 180 of the study. **RESULTS:** After a planned interim analysis, the data and safety monitoring board recommended that the studies be discontinued because data from the first 107 patients indicated that it was highly unlikely that a significant difference in treatment efficacy between the groups would be observed with the planned full enrollment of 260 patients. Base-line assessments documented severe impairment in the patients' health-related quality of life. In intention-to-treat analyses, there were no significant differences in the outcomes with prolonged antibiotic treatment as compared with placebo. Among the seropositive patients who were treated with antibiotics, there was improvement in the score on the physical-component summary scale of the SF-36, the mental-component summary scale, or both in 37 percent, no change in 29 percent, and worsening in 34 percent; among seropositive patients receiving placebo, there was improvement in 40 percent, no change in 26 percent, and worsening in 34 percent ($P=0.96$ for the comparison between treatment groups). The results were similar for the seronegative patients. **CONCLUSIONS:** There is considerable impairment of health-related quality of life among patients with persistent symptoms despite previous antibiotic treatment for acute Lyme disease. However, in these two trials, treatment with intravenous and oral antibiotics for 90 days did not improve symptoms more than placebo.

Krupp LB, Hyman LG, Grimson R, Coyle PK, Melville P, Ahnn S, Dattwyler R, Chandler-B. Study and treatment of post Lyme disease (STOP-LD): A randomized double masked clinical trial. Neurology. 2003 Jun 24;60(12):1923-30

This is a single-center randomized double-masked placebo-controlled trial involving 55 patients with Lyme disease with persistent severe fatigue at least 6 or more months after antibiotic therapy. Patients were randomly assigned to receive 28 days of IV ceftriaxone or placebo. The primary clinical outcomes were improvement in fatigue, defined by a change of 0.7 points or more on an 11-item fatigue questionnaire, and improvement in cognitive function (mental speed), defined by a

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Lyme Disease Medical Policy

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change of 25% or more on a test of reaction time. The primary laboratory outcome was an experimental measure of CSF infection, outer surface protein A (OspA). Outcome data were collected at the 6-month visit. Results showed patients assigned to ceftriaxone showed improvement in disabling fatigue compared to the placebo group (rate ratio, 3.5; 95% CI, 1.50 to 8.03; $p = 0.001$). No beneficial treatment effect was observed for cognitive function or the laboratory measure of persistent infection. The study concluded that because fatigue (a nonspecific symptom) was the only outcome that improved and because treatment was associated with adverse events, this study does not support the use of additional antibiotic therapy with parenteral ceftriaxone in post-treatment, persistently fatigued patients with Post Lyme syndrome.

Medical Letter on Drugs and Therapeutics Treatment of Lyme Disease
May 23, 2005; (1209) pp. 41-42

"Use of repellents and avoidance and early removal of ticks are the first steps in prevention of Lyme disease. In highly endemic areas, when an engorged Ixodes scapularis tick is attached for at least 48 hours, prophylaxis with a single dose of doxycycline would be reasonable in adults and children at least 8 years old. With a less compelling indication, it would be reasonable not to prescribe antibiotics unless erythema migrans develops. Recommended doses of antibiotics cure almost all patients with erythema migrans without complications. **Antibiotic therapy is not recommended for patients with a history of appropriately treated Lyme disease and persistent subjective symptoms.**"

Practice Guidelines for the Treatment of Lyme Disease, Guidelines from the Infectious Diseases Society of America. Clinical Infectious Diseases 2000;31(Suppl 1):S1-14.

An expert panel provides evidence-based standards of diagnosis and treatment of Lyme disease. The panel finds that there is insufficient evidence to regard "post-Lyme disease syndrome" as a separate diagnostic entity.

Steere AC, et al. The emergence of Lyme disease J Clin Invest. 2004 April 15; 113 (8): 1093–1101.

"A counterculture has emerged regarding chronic Lyme disease. In contrast with the findings of evidence-based medicine, some people believe that the tests for Lyme disease are often inaccurately negative, and that antibiotic therapy is necessary for months or years to suppress the symptoms of this often incurable illness. A number of investigators at academic medical centers have reported series of patients referred for chronic Lyme disease in which the majority of patients had pain or fatigue syndromes with little or no evidence of past or present *B. burgdorferi* infection. Prolonged antibiotic therapy may be harmful. In studies of patients with unsubstantiated Lyme disease, minor side effects were common, prolonged ceftriaxone therapy sometimes resulted in biliary complications, and in one reported case, the prolonged administration of cefotaxime resulted in death. Furthermore, prolonged use of antibiotics was recently associated with an increased risk of breast cancer. Although antibiotic use may not be causally related to cancer, this observation reinforces the advisability of prudent use of antibiotics." "Among *B. burgdorferi*-infected patients, a prior history of depression or anxiety seems to be a risk factor for the development of chronic Lyme disease."

Wormser GP, Nowakowski J, Nadelman RB. Duration of treatment for Lyme borreliosis: time for a critical reappraisal. Wien Klin Wochenschr. 2002 Jul 31;114(13-14):613-5

This review discusses the duration of antibiotic therapies. "The presumptions that post-treatment subjective complaints, which occur in a minority of patients, may be reduced by increasing the duration of initial therapy or ameliorated by a repeat course of parenteral or oral antimicrobials, have not been supported by recent clinical trials."

Wormser GP, Ramanathan R, Nowakowski J, et al. Duration of antibiotic therapy for early Lyme disease. Ann Intern Med. 2003;138(9):697-704.

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In a randomized, double-blind, placebo-controlled trial, there was no significant difference in response rates and long-term outcomes between patients with early Lyme disease allocated to receive 10 or 20 days of oral doxycycline. Follow-up data were collected at 20 days, 3 months, 12 months, and 30 months following treatment. Patients at least 16 years of age with erythema migrans = 5 cm in diameter who presented for evaluation at a single center specializing in Lyme disease diagnosis were eligible to participate in this trial if there was no evidence of meningitis. Those enrolled were assigned to 1 of 3 treatment groups: a 10-day course of doxycycline 100 mg twice daily preceded by a single intravenous 2-g dose of ceftriaxone (n=60), 10 days (n=61) of the doxycycline alone, or 20 days (n=59) of the doxycycline alone. To preserve blinding, patients in the 10-day treatment groups were given identical placebo capsules to take for another 10 days, while those in the two groups not given ceftriaxone began the protocol with placebo intravenous injections. Baseline characteristics among patients in the three treatment groups were well balanced with the exception of duration of erythema migrans. At 20 days follow-up, approximately two thirds of patients in each treatment group had a complete response to treatment, defined as resolution of erythema migrans and associated symptoms, as well as full restoration of health to pre-Lyme disease status. After 30 months, 83.9% to 90.3% of the patients in each treatment group had a complete response, which at that point in time also included the absences of objective rheumatologic, cardiac, and neurologic manifestations of Lyme disease. A single patient failed to respond to treatment (10-day doxycycline) and developed cerebrospinal fluid pleocytosis that improved after 14 days of ceftriaxone. Adverse treatment-related side effects were significantly more frequent among patients given ceftriaxone than in those injected with placebo. These results suggest that extended courses of antibiotic therapy for uncomplicated Lyme disease is not necessary. Outcomes apply only to those individuals with Lyme disease caused by the single genospecies of *B. burgdorferi*, found in the United States, and who are free from nervous system or musculoskeletal involvement.

Source: Hayes Technology Alert, June 2003

Bibliography

Bunikis J, Barbour AG. Laboratory Testing for Suspected Lyme Disease. Medical Clinics of North America, Vol. 86, No. 2, March 2002.

Caution Regarding Testing for Lyme Disease JAMA April 20, 2005 Vol.293 No.15 pg. 1853

CDC Recommendations for the use of lyme disease vaccine recommendations of the advisory committee on immunization practices (ACIP) June 4 1999/ 48(RR07);1-17. available on the www at <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr4807a1.htm> accessed 7/12/2005

CDC Notice to readers recommendations for test performance and interpretation from the second national conference on serologic diagnosis of Lyme disease. Aug. 11, 1995 44(31);590-591.

Coyle PK, Schutzer SE. Neurologic Aspects of Lyme Disease. Tick-Borne Diseases. Medical Clinics of North America Vol 86 no.2 March 2002

Fleming RV, et al. Pre-treatment and post-treatment assessment of the C(6) test in patients with persistent symptoms and a history of Lyme borreliosis Eur J Clin Microbiol Infect Dis. 2004;23(8):615-618.

Goldman: Cecil Textbook of Medicine, 21st ed. Copyright 2000 W.B. Saunders Company, 1757-1761.

Hayes EB, Fleisher J. How Can We Prevent Lyme Disease? *New England Journal of Medicine* 348;24:2424-2430.

Hayes EB, Piesman J. How Can We Prevent Lyme Disease. *N Engl J med* 2003;348:2424-30.

Hayes Technology Alert, June 2003

1. The following table gives the number of hours worked by each of the 100 workers.

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Hayes Technology Assessment Lyme Disease, Laboratory Diagnosis July 2003 Hayes Update Search 8/2004

Hengge U, Tannapfel A, et. al., Lyme borreliosis, *The Lancet Infectious Diseases*, Volume 3, Number 8, August 2003.

Kaplan RF, Trevino RP, Johnson GM, Levy L, Dombush R, Hu LT, Evans J, Weinstein A, Schmid CH, Klempner MS. Cognitive function in post-treatment Lyme disease Do additional antibiotics help? *Neurology*. 2003 Jun 24;60(12):1916-22

Klempner MS, Hu LT, Evans J, Schmid CH, Johnson GM, Trevino RP, Norton D, Levy L, Wall D, McCall J, Kosinski M, Weinstein A. Two controlled trials of antibiotic treatment in patients with persistent symptoms and a history of Lyme disease. *N Engl J Med*. 2001 Jul 12;345(2):85-92.

Krupp LB, Hyman LG, Grimson R, Coyle PK, Melville P, Ahnn S, Dattwyler R, Chandler B. Study and treatment of post Lyme disease (STOP-LD): A randomized double masked clinical trial. *Neurology*. 2003 Jun 24;60(12):1923-30

Medical Letter on Drugs and Therapeutics Treatment of Lyme Disease
May 23, 2005; (1209) pp. 41-42

Meyerhoff J. Johns Hopkins 10/2004 Lyme Disease

Practice Guidelines for the Treatment of Lyme Disease, Guidelines from the Infectious Diseases Society of America. *Clinical Infectious Diseases* 2000;31(Suppl 1):S1-14.

Reed KD Marshfield Clinic Laboratory Testing for Lyme Disease Feb 2002

Rothermel H, et al. *Pediatrics* Aug 2001 Optic Neuropathy in children with Lyme Disease

Steere AC, Dhar A, Hernandez J, et al. Systemic symptoms without erythema migrans as the presenting picture of early Lyme Disease. *America Journal of Medicine*, Vol. 114, No. 1, January 1, 2003.

Steere AC. Lyme Disease. *New England Journal of Medicine*, Vol. 345, NO. 2, July 12, 2001, 115-125.

Steere AC, et al. The emergence of Lyme disease *J Clin Invest*. 2004 April 15; 113 (8): 1093-1101

University Utah ARUP labs 2004 http://www.aruplab.com/guides/clt/tests/clt_a110.jsp accessed 10/6/04

Wormser GP, Nowakowski J, Nadelman RB. Duration of treatment for Lyme borreliosis: time for a critical reappraisal. *Wien Klin Wochenschr*. 2002 Jul 31;114(13-14):613-5

Wormser GP, Ramanathan R, Nowakowski J, et al. Duration of antibiotic therapy for early Lyme disease. *Ann Intern Med*. 2003;138(9):697-704.

Clinical Administration Guidelines

Introduction

Lyme disease is a multi-system disease caused by the spirochete bacterium, *Borrelia burgdorferi*. These bacteria are transmitted to humans by the bite of an infected tick (usually *Ixodes* sp.). Both deer and rodent hosts are necessary to maintain the enzootic cycle of *B. burgdorferi*. The *I. scapularis* tick may also transmit *Anaplasma phagocytophilia*, which causes human granulocytic ehrlichiosis (HE), and babesiosis, which is caused by a red blood cell protozoan. Lyme disease is the most common vectorborne disease in the United States. Over 90% of cases come from Connecticut, Rhode Island, Pennsylvania, Delaware, New Jersey, Maryland, Massachusetts

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and Wisconsin. Its clinical hallmark is an early expanding skin lesion, which can be followed months to years later by neurologic, cardiac or joint abnormalities. All stages of Lyme Disease respond to antibiotics but early stage treatment has the most favorable results. Some providers believe that vague constitutional symptoms and fatigue are caused by lingering infection with the Lyme spirochete. Long-term antibiotic treatment for chronic symptoms is not supported by medical literature.

Please refer to medical policy for signs and symptoms.

Required documentation for referral**Medical Policy #185A****Clinical Documentation / Medical Records Recommended for this review**

1. Contract language for – Medical Necessity / Experimental / Investigational
2. MD office notes documenting symptoms/ current and previous treatments
3. Lab and x-ray specific to treated medical condition (i.e., Elisa, Western Blot), all medications prescribed

Clinical Decision Making Guidelines

See decision trees

- Oral Antibiotics
- Intravenous Antibiotics

Please refer to Treatment Recommendations, Infectious Disease Society of America within medical policy.

Related Coding**CPT**

86666 - Ehrlichia

84181 - Protein; western blot, with interpretation and report, blood or other body fluid
 84182 - Protein; western blot, with interpretation and report, blood or other body fluid, immunological probe for band identification, each

*86617 - *Borrelia burgdorferi* (Lyme disease) confirmatory test (e.g., western blot or immunoblot)

*86618 - *Borrelia burgdorferi* (Lyme disease)

*86619 - *Borrelia* (relapsing fever)

*87475 - *Borrelia burgdorferi*, direct probe technique

*87476 - *Borrelia burgdorferi*, amplified probe technique

*87477 - *Borrelia burgdorferi*, quantification.

HCPCS

No codes pertinent to policy

ICD-9 Procedure

No codes pertinent to policy

ICD-9 Diagnosis

082.40 - Ehrlichiosis, unspecified

082.41 - Ehrlichiosis chaffeensis (*E.chaffeensis*)

082.49 - Other ehrlichiosis

*088.81 - Lyme disease

088.82 - Babesiosis

088.89 - Other specified arthropod-borne diseases

088.9 - Arthropod-borne disease, unspecified

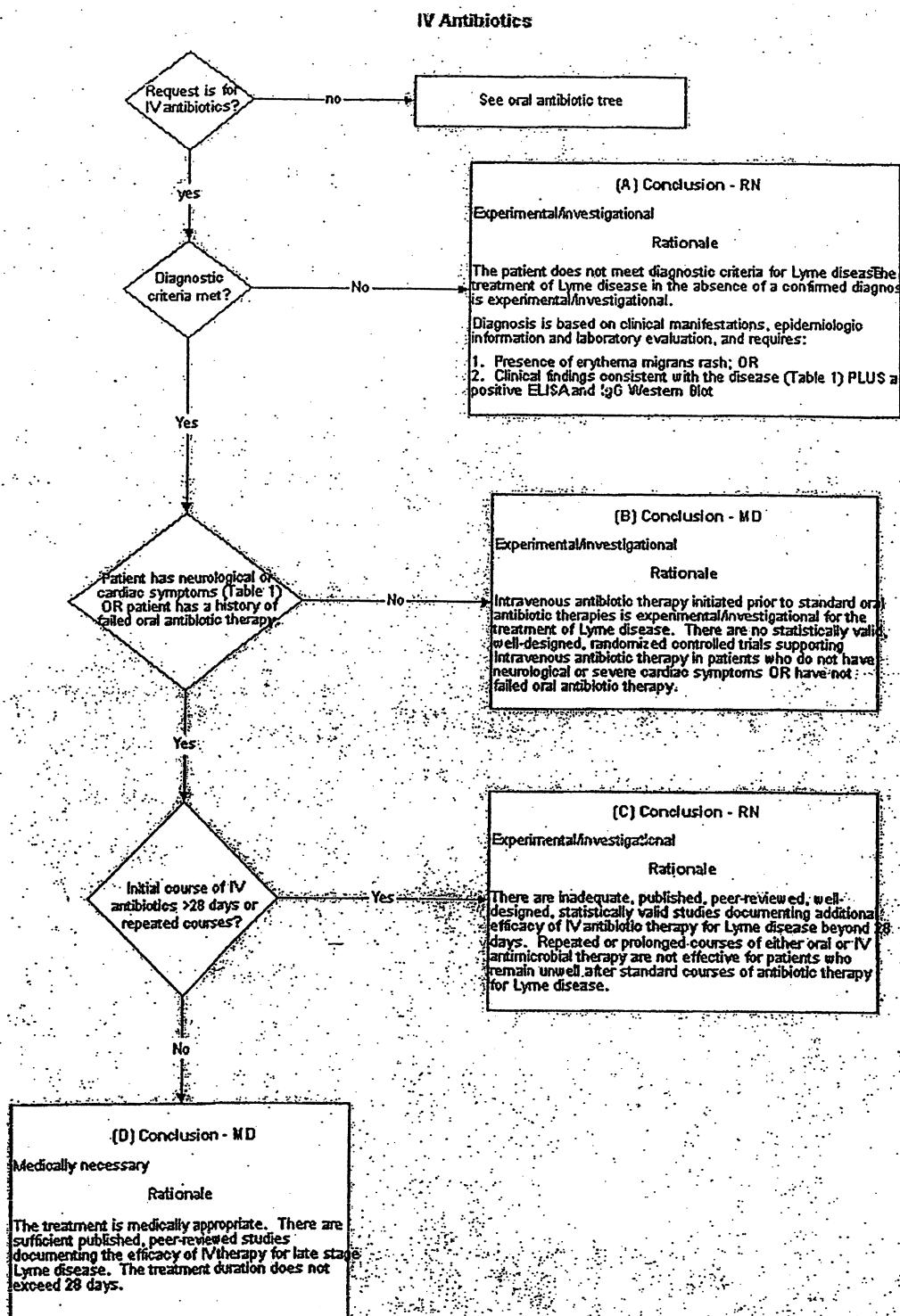
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Lyme Disease Medical Policy

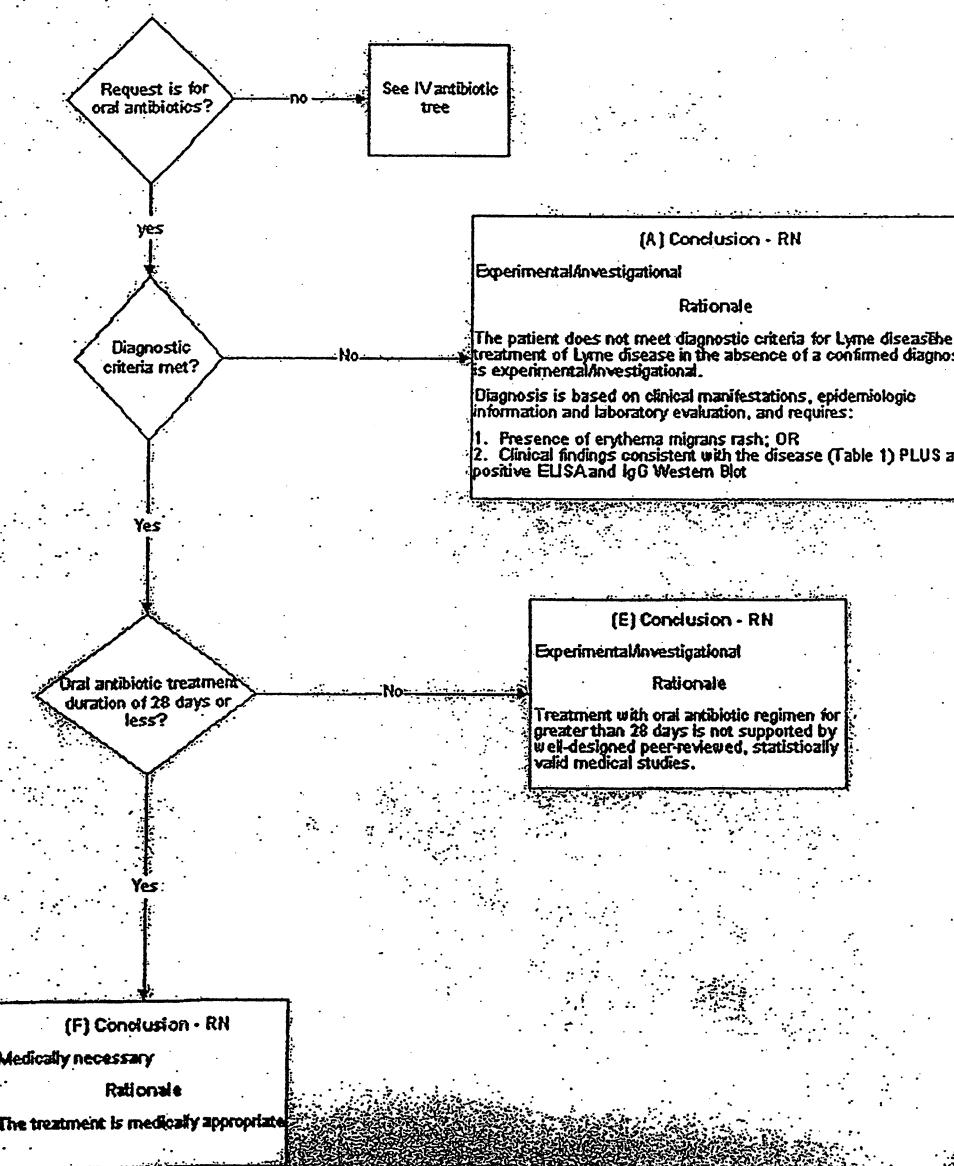
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*Codes recommended for inclusion on HSGR

Decision Tree



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Oral Antibiotics:

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EXHIBIT 9



ASSURANT
Health

501 W. Michigan Avenue
P.O. Box 3264
Milwaukee, WI 53201-3264
Phone: 800-454-5105

September 15, 2005

www.assuranthealth.com

Talia Hinman
% Melinda Hinman
3643 Scott Rd.
Hood River, OR 97031

FILE COPY

Claimant: Talia Hinman
Policyholder: Melinda Hinman
Policy: 539153-9-D00
Reference #: 052563810

Provider: N/A
Facility: Immungenex, Inc.
Supplier: N/A

Treatment/Service: 86617 / 86256 / 99001 / 86682

Date(s) of Service Not Certified: 3/31/05 – 6/23/05

Reason Treatment/Service Not Certified: Experimental and Investigational

Screening Criteria: Generally Accepted Medical Principles

Dear Talia Hinman:

The Health Management Department has received notice that the member named above has received medical service(s). The case was referred to our Physician Advisor. Based upon the medical information provided, we have determined that the requested treatment or service as indicated above is Experimental and Investigational.

This service meets the definition of experimental and investigational in your contract and thus, is excluded by your contract. The applicable exclusion language states: We will not cover charges: For any and all services, treatments or supplies related to, or in association with a course of treatment that is Experimental or Investigational, as defined in this Certificate. We will also not cover any complications which result from Experimental or Investigational course of treatment.

The clinical rationale regarding this decision is: 17 y/o female was apparently first seen 10-12-04. The medical record does not document a chief complaint, any symptoms or reason for visit. The medical record does not support provider assessment of probable Lyme disease in this patient who does not live in a Lyme disease area: there is no documentation of tick exposure; there is no documentation of symptoms; there is no documentation of a thorough medical examination including a neurological examination. The medical record does document an E/I practice with plan for 2-4 months of antibiotics and testing for heavy metals without documentation of exposure, symptoms, or physical examination findings. Lyme IgG western blot test did not support diagnosis of Lyme disease. Patient had apparently tested positive 5-04 for 4 of 10 bands

Assurant Health markets products underwritten by Time Insurance Company, Union Security Insurance Company and John Alden Life Insurance Company.

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and equivocal for 3 bands. For 3-29-05 date of service: there is no physical examination; there is no history of recurrent tick exposure to document necessity of repeat Western Blot and other infectious organisms tests done 3-29-05. The medical record does not support 99215 for 3-29-05 date of service. All services 11-16-04 through 6-21-05 are related to an E/I practice pattern; certificate of insurance excludes coverage of E/I services.

You have the right to appeal this decision. Please see the enclosure for the appeal procedure. This decision does not alter, limit or restrict in any manner the attending physician's ultimate patient care responsibility.

The screening criteria listed above was relied upon in making this determination. If your coverage with us is through an employee benefit plan that is established or maintained by an employer or employee organization, you have the right to request a copy of the screening criteria, which will be provided to you free of charge.

If you have any questions regarding this decision or your right to appeal, you may contact us by:

- Writing to us at:
Assurant Health
Health Management
PO Box 3264
Milwaukee, WI 53201-3264
- Faxing us at 414-299-7555
- Calling the Appeals Coordinator at 800-454-5105, Ext. 6239

Sincerely,

Health Management Department

cc: Immungenex, Inc.
797 San Antonio Rd.
Palo Alto, CA 94303

Enclosure: Insured's Right to Appeal - OR

DN/tg

AR1555

EXHIBIT 10



**ASSURANT
Health**

501 W. Michigan Avenue
P.O. Box 3264
Milwaukee, WI 53201-3264
Phone: 800-454-5105

March 15, 2006

www.assuranthealth.com

Melinda Hinman
3643 Scott Road
Hood River, OR 97031

Claimant: Talia Hinman **Policyholder:** Melinda Hinman
Providers: Providence Hood River Memorial Hospital
Christine Green, MD
Janice Journeau, MD
Immungenex, Inc.
Laboratory Corporation of America
Policy #: 539153-9-D00
Reference #'s: 052563800, 052563807, 052563810, 053364110
Dates of Service: 10/15/04 - 10/31/05
Treatment/Services: Office visits, laboratory tests and medication administration

Type of Review Performed: Level I Appeal Review

Screening Criteria: Internally Developed Medical Criteria; #185 A, Lyme Disease

Dear Melinda Hinman:

This letter is in response to your appeal of the adverse decision of the treatment or services identified above. Related medical records and submitted correspondence have been reviewed.

Please note that as part of our review, all currently denied services were reviewed. The specific services denied under Reference # 052563802 were not a part of this review. You will receive notification of that Level II appeal determination under separate cover.

Your appeal was reviewed by a physician who is board certified in Internal Medicine. Based on the medical information submitted, it was determined that the adverse decision of the above treatment or services will be modified as follows:

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- Diagnostic tests performed on 10/15/04 are approved as medically necessary including: 86256 Fluorescent noninfectious agent screen, 86611 antibody Bartonella, and 87476 infectious agent detection, Borrelia burgdorferi; and
- All other services / treatment remain denied as experimental, and
- Services required for management of complications of experimental treatment are not covered

The Certificate of Coverage definition of experimental or investigational services states:

"A service or supply is Experimental or Investigational when We determine that it is:
1. not of proven benefit for the particular diagnosis or treatment of a particular condition, as established by any of the reference compendia cited below or; 2. not generally recognized by the medical community as effective or appropriate for the particular diagnosis or treatment of a particular condition; or 3. provided or performed in special settings for research purposes or under a controlled environment or clinical protocol.

We will apply the following five criteria in determining whether services or supplies are Experimental or Investigational:

1. Any medical device, drug, or biological product must have received final approval to be marketed by the FDA for the particular diagnosis or condition. Any other approval; granted as an interim step in the FDA regulatory process, e.g., an Investigational Device Exemption or an Investigational New Drug Exemption, is not sufficient. Once FDA approval has been granted for a particular diagnosis or condition, use of the medical device, drug or biological product for another diagnosis or condition will require that one or more of the following established reference compendia recognize the usage as appropriate medical treatment:

- a. The American Medical Association Drug Evaluations;
- b. The American Hospital Formulary Drug Information; or
- c. The United States Pharmacopeia Drug Information.

As an alternative to such recognition in one or more of the compendia, the usage of the drug will be recognized as appropriate if it is recommended by a clinical study and recommended by a review article in a major peer-reviewed professional journal. A medical device, drug or biological product that meets the above tests will not be considered Experimental or Investigational.

In any event, any drug which the FDA has determined to be contraindicated for the specific treatment for which the drug has been prescribed will be considered Experimental or Investigational.

2. Conclusive evidence from the published peer-reviewed medical literature must exist that the technology has a definite positive effect on health outcomes; such evidence must include well-designed investigations that have been reproduced by non-affiliated authoritative sources, with measurable results, backed up by the positive endorsements of national medical bodies or panels regarding scientific efficacy and rationale.
3. Demonstrated evidence as reflected in the published peer-reviewed medical literature must exist that, over time, the technology leads to improvement in health outcomes, i.e., the beneficial effects outweigh any harmful effects.
4. Proof as reflected in the published peer-reviewed medical literature must exist that the technology is at least as effective in improving health outcomes as established technology, or is usable in appropriate clinical contexts in which established technology is not employable. And
5. Proof as reflected in the published peer-reviewed medical literature must exist that improvements in health outcomes, as defined in item 3 above, is possible in standard conditions of medical practice, outside clinical investigatory settings."

Claims for the authorized services have been forwarded for processing. Claim payments will be issued in accordance with the terms, limitations, conditions, and exclusions in the Certificate of Coverage.

The clinical rationale for the decision is as follows:

At issue is whether services including certain office visits, laboratory tests and medication administration services for presumed Lyme disease are excluded from coverage as Experimental/Investigational services. Review of the medical records does not yield information meeting the accepted definition for Lyme disease. The patient lives in an area where she could be exposed to infection with Lyme disease, but the record includes no documentation of an erythema migrans rash and serologic tests do not meet the recommended criteria for positivity. The documented clinical symptoms might occur with a wide variety of conditions. Treatment with oral antibiotics for presumed Lyme disease is documented, but exceeds duration of administration, having started on or about October 12, 2004, and continued at least to January 4, 2005. Intravenous antibiotics were administered in two courses including July 19, 2005 to September 30, 2005, and October 1, 2005 to October 31, 2005 for a total of more than three months of treatment. In the absence of meeting established diagnostic criteria for Lyme disease, treatment for Lyme disease is experimental / investigational. In addition, intravenous antibiotic treatment for Lyme disease beyond 28 days is of unproven efficacy and is experimental / investigational. Services that were for the provision of experimental / investigational therapy including intravenous services,

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office visits and laboratory monitoring are excluded from coverage. Services required for management of complications of experimental / investigational treatment are excluded from coverage.

The screening criteria listed above was relied upon in making this determination. If your coverage with us is through an employee benefit plan that is established or maintained by an employer or employee organization, you have the right to request a copy of the screening criteria, which will be provided to you free of charge.

This decision does not alter, limit or restrict in any manner the attending physician's ultimate patient care responsibility.

Enclosed is specific information on your right to appeal the adverse decision and how to contact us if you have any further questions.

Sincerely,



Chris Gunta, RN
Appeal Coordinator
Health Management Department

cc: Providence Hood River Memorial Hospital
811 13th Street
PO Box 149
Hood River, OR 97031

Christine Greene, MD
450 Sutter Street, Suite 1504
San Francisco, CA 94108

Janice Journeau, MD
810 13th Street
Hood River, OR 97031

Immungenex, Inc.
797 San Antonio Road
Palo Alto, CA 94303

Laboratory Corporation of America
1447 Yourk Court
Burlington, NC 27215

Enclosure: Insured's Right to Appeal

**Assurant Health
Right to Appeal - Oregon
Group Plans**

You have the right to appeal the adverse decision or designate a representative to appeal for you.

The following information describes the appeal procedure.

Level I Appeal Request

Assurant Health allows you, your provider, or facility rendering services 180 calendar days after the receipt of the adverse decision to request a Level I appeal.

- Include in your request any additional medical information that you feel is pertinent to your case.
- We will send you written acknowledgement of your request.
- The Level I Appeal review will be completed and written notification of the decision will be sent to you within thirty (30) calendar days of initiation of the appeal process.
- Send the request either in writing, by fax or telephone to:

Assurant Health
Health Management Appeals Department
P.O. Box 3264
Milwaukee, WI 53201-3264

Telephone: 800-454-5105, ext. 6239
Fax: 414-299-7555, Attention: Health Management Appeals Department

Level II Appeal Request

If you wish to appeal the Level I Appeal decision, you or your designated representative may request a Level II Appeal Panel review. This request must be received in writing at the above address within sixty (60) days of the date of the Level I Appeal decision letter.

- Include in your request any additional medical information that you feel is pertinent to your case.
- We will send you written acknowledgement of your request.
- You shall have the opportunity to appear before the Appeal Panel.
- The Level II Appeal Panel review will be completed within thirty (30) calendar days of the receipt of your request. We will notify you in writing of the decision.

If you have not yet received the services you are appealing:

For pre-service appeals, all of the steps outlined above under Level I and Level II will be combined into one final appeal process and will be completed within 30 calendar days of receipt of the appeal request. "Pre-Service" means any claim for a benefit under a group health

plan with respect to which the terms of the plan condition receipt of the benefit, in whole or in part, on approval of the benefit in advance of obtaining medical care.

Our internal appeals process will be exhausted upon completion of the pre-service appeal or the Level II Appeal Panel decision. If your coverage with us is through an employee benefit plan that is established or maintained by an employer or employee organization, after exhausting the internal appeal processes, you have the right to bring a civil action under ERISA section 502(a).

If your coverage with us is through an employee benefit plan that is established or maintained by an employer or employee organization, you may have reasonable access to all documents, records and other information relevant to your claim or request for benefits and obtain a copy of such information free of charge, upon request.

Independent External Review

If you are dissatisfied with the Level II Appeal Panel decision, you may have the right to file a request for an independent external review. You may apply for an independent external review directly with us at the above listed address after all internal appeals processes have been exhausted. In order to qualify for this review, the final adverse decision by Assurant Health must concern whether a course or plan of treatment is medically necessary, experimental or investigational, or an active course of treatment for purposes of obtaining continuity of care under Oregon law. You must request an external review not later than the 180th day after receipt of Assurant Health's final written decision. The request must include a signed waiver granting the independent external review organization access to your medical records.

Within 2 business days of receiving your request, we will send the request to the Oregon Insurance Division, which will assign an independent review organization (IRO).

The IRO will review the dispute and issue a written decision. An IRO has 30 days to issue a decision after you apply to the insurer for an external review.

You may qualify for an expedited external review if a provider with an established clinical relationship to you certifies in writing and provides supporting documentation that the ordinary time period for external review would seriously jeopardize your life or health or your ability to regain maximum function. Also, you qualify for an expedited external review if your request is regarding mastectomy-related services. In this case, we will inform the Insurance Division that the referral is expedited. If you qualify for an expedited review, a decision shall be issued by the IRO within three days of the request.

Assurant Health is not bound by the decisions of independent review organizations. Assurant Health may follow nonetheless a decision by an independent review organization. If we do not comply with the decision, you have a right to sue us.

You have the right to file a complaint or seek other assistance from the Oregon Insurance Division.

Assistance is available:

By calling 503- 947-7984;

By writing to the Oregon Insurance Division
Consumer Protection Unit
350 Winter St. NE, Rm 440-2
Salem, Oregon 97301-3883
Fax 503- 378-4351
888- 877-4894 (toll-free message phone)
E-mail address: dcbs.insmail@state.or.us;

Through the internet at <http://www.cbs.state.or.us/external/ins/>

EXHIBIT 11



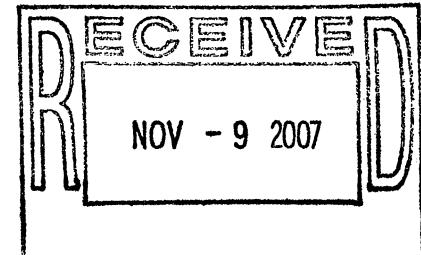
**ASSURANT
Health**

501 W. Michigan Avenue
P.O. Box 3264
Milwaukee, WI 53201-3264
Phone: 800-454-5105

November 6, 2007

www.assuranthealth.com

Haglund, Kelley, Horgren, Jones, & Wilder
Attn: Christopher Lundberg
One Main Place
101 SW Main St., Suite 1800
Portland, OR 97204



Claimant: Talia Hinman
Policyholder: Melinda Hinman
Policy #: 539153-9-D00
Dates of Service: 10/15/04-10/31/05

Reference #: 052563800	Provider: Christine Green, M.D.
Reference #: 052563807	Provider: Laboratory Corp. of America
Reference #: 052563810	Provider: Immungenex
Reference #: 053364110	Provider: Janice Journeau, M.D.

Treatment/Services: Office visits, laboratory tests, and IV antibiotics

Type of Review Performed: Level II Appeal Panel Review

Clinical Criteria: Internally Developed Medical Criteria [Lyme Disease, Medical Policy #185A]

Dear Mr. Lundberg:

This is in response to your request for a Level II Appeal Panel review of the adverse decision of the treatment or services identified above. We would like to thank Ms. Weiss, the representative from your law firm, as well as Melinda and Talia Hinman for attending the grievance panel.

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All file information and medical records submitted to us were reviewed by a physician who is board certified in Family Medicine and licensed in the state of Oregon. It was also reviewed by an outside consultant (MCMC) who is board certified in Internal Medicine and Infectious Disease. Based on these reviews and the review of the Panel on November 5, 2007, the previous decision has been upheld as experimental or investigational.

The clinical rationale for the decision is as follows:

I do not believe that the claimant has Lyme disease in any stage. Her Western blot test is negative. There is no documentation of tick exposure or history of erythema migrans. Her clinical course is quite atypical for Lyme disease. Essentially she has no significant supportive evidence of having Lyme disease. Therefore intrinsically the treatment of diagnosis- unsupported Lyme disease with this regimen is experimental/investigational. In addition, there is no evidence-based medicine that supports the approach of prolonged treatment of Lyme disease. Even if the patient did have Lyme disease there is no evidence based medicine that treatment for longer than one month has any improvement in outcome. The information submitted in the form of copies of articles with the appeal does not present evidence-based medicine that is contrary to my previously expressed opinion. In general, the articles were based on animal models, very limited series involving patients.

Probably the best-conducted study that was submitted, was a randomized double mast clinical trial (Krupp LB, et al. A randomized double masked clinical trial neurology, 2003 60, 1923-1930.) The conclusion of this trial that there was no beneficial treatment effect of prolonged treatment upon cognitive function or the laboratory measurements of persistent infection. The study does not support the use of additional antibiotic therapy with parenteral ceftriaxone and posttreatment, persistently fatigued patients with "Post Lyme Syndrome".

My conclusion is that the submitted literature either cited studies that are of limited validity or are indeed as the above-cited one contradict the patient's position or are essentially irrelevant to the question at hand. The requested Lyme disease treatment is considered experimental/investigational.

CLINICAL SUMMARY:

Review of a physician's request to treat the patient with prolonged antibiotic therapy for purported Lyme disease.

REFERENCE:

New Guidelines for Lyme Disease Prevention Clinical Infectious Diseases October 2006.

The Certificate of Coverage definition of experimental or investigational states:

"Experimental or Investigational:

A service or supply is Experimental or Investigational when We determine that it is:

1. not of proven benefit for the particular diagnosis or treatment of a particular condition, as established by any of the reference compendia cited below; or
2. not generally recognized by the medical community as effective or appropriate for the particular diagnosis or treatment of a particular condition; or
3. provided or performed in special settings for research purposes or under a controlled environment or clinical protocol.

We will apply the following five criteria in determining whether services or supplies are Experimental or Investigational:

1. Any medical device, drug, or biological product must have received final approval to be marketed by the FDA for the particular diagnosis or condition. Any other approval, granted as an interim step in the FDA regulatory process, e.g., an Investigational Device Exemption or an Investigational New Drug Exemption, is not sufficient. Once FDA approval has been granted for a particular diagnosis or condition, use of the medical device, drug or biological product for another diagnosis or condition will require that one or more of the following established reference compendia recognize the usage as appropriate medical treatment:

- a. The American Medical Association Drug Evaluations;
- b. The American Hospital Formulary Drug Information; or
- c. The United States Pharmacopeia Drug Information.

As an alternative to such recognition in one or more of the compendia, the usage of the drug will be recognized as appropriate if it is recommended by a clinical study and recommended by a review article in a major peer-reviewed professional journal. A medical device, drug or biological product that meets the above tests will not be considered Experimental or Investigational.

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In any event, any drug which the FDA has determined to be contraindicated for the specific treatment for which the drug has been prescribed will be considered Experimental or Investigational.

2. Conclusive evidence from the published peer-reviewed medical literature must exist that the technology has a definite positive effect on health outcomes; such evidence must include well-designed investigations that have been reproduced by non-affiliated authoritative sources, with measurable results, backed up by the positive endorsements of national medical bodies or panels regarding scientific efficacy and rationale.
3. Demonstrated evidence as reflected in the published peer-reviewed medical literature must exist that, over time, the technology leads to improvement in health outcomes, i.e., the beneficial effects outweigh any harmful effects.
4. Proof as reflected in the published peer-reviewed medical literature must exist that the technology is at least as effective in improving health outcomes as established technology, or is usable in appropriate clinical contexts in which established technology is not employable. And
5. Proof as reflected in the published peer-reviewed medical literature must exist that improvements in health outcomes, as defined in item 3 above, is possible in standard conditions of medical practice, outside clinical investigatory settings."

The General Medical Charges portion of the Certificate of Coverage states, in part:

"We will not cover charges for ...

2. Any and all services, treatments or supplies related to, or in association with, a course of treatment that is Experimental or Investigational, as defined in this certificate..."

The following information was used in the review:

- Letter of Level II Appeal request from Christopher Lundberg dated 7/31/07.
- Binder with 35 exhibits submitted In the Matter of the Level II Appeal of Talia Hinman
- Fax cover sheet from Christopher Lundberg dated 6/18/07
- Letter from Christopher Lundberg dated 6/18/07

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- Letter from Christopher Lundberg dated 7/6/06
- Fax cover sheet from Christopher Lundberg dated 6/9/06
- Letter from Christopher Lundberg dated 6/9/06
- Authorized Representative Forms signed 5/25/06
- Level II Appeal request from Christopher Lundberg dated 5/15/06
- Fax cover Sheet from Christopher Lundberg dated 5/15/06
- Binder/compendium of information submitted by Dale and Melinda Hinman with cover sheet dated -2/27/06 regarding Level I Appeal for Talia Hinman
- Care corner X-Ray report dated 1/11/99
- Labcorp laboratory reports for collection dates 10/13/04 - 6/21/05
- IGeneX laboratory reports dated for draw dates 10/13/04 - 6/21/05
- Hood River Memorial Hospital diagnostic reports dated 7/17/97 - 9/13/05
- Urinalysis results dated 5/18/93 - 7/17/97
- National Health Laboratories lab report dated 1/17/95
- Oregon State Public Health Laboratory Parasitology Report for collection date 7/17/97
- Columbia Gorge Family Medicine patient records dated 10/16/92 -9/22/05
- Greenoaks Medical Clinic patient records dated 10/12/04 - 6/21/05

The clinical criteria listed on page one was relied upon in making this determination. If your coverage with us is through an employee benefit plan that is established or maintained by an employer or employee organization, you have the right to request a copy of the clinical criteria, which will be provided to you free of charge.

This letter serves as notification that the internal appeals process has been exhausted. This decision does not alter, limit or restrict in any manner the attending physician's ultimate patient care responsibility.

Enclosed is specific information on your right for requesting an independent external appeal of this decision as required by your state and how to contact us if you have any further questions.

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Sincerely,



Jessie Tennie, RN, BSN
Health Management Department

cc: Providence Hood River Memorial Hospital
811 13th St.
P.O. Box 149
Hood River, OR 97031

cc: Christine Green, M.D.
450 Sutter St., Suite 1504
San Francisco, CA 94108

cc: Janice Journeau, M.D.
810 13th St.
Hood River, OR 97031

cc: Immungenex, Inc.
797 San Antonio Rd.
Palo Alto, CA 94303

cc: Laboratory Corporation of America
1447 Yourk Court
Burlington, NC 27215

Enclosure: Insured's Right to Appeal

**Assurant Health
Right to Appeal - Oregon
Group Plans**

You have the right to appeal the adverse decision or designate a representative to appeal for you.

The following information describes the appeal procedure.

Level I Appeal Request

Assurant Health allows you, your provider, or facility rendering services 180 calendar days after the receipt of the adverse decision to request a Level I appeal.

- Include in your request any additional medical information that you feel is pertinent to your case.
- We will send you written acknowledgement of your request.
- The Level I Appeal review will be completed and written notification of the decision will be sent to you within thirty (30) calendar days of initiation of the appeal process.
- Send the request either in writing, by fax or telephone to:

Assurant Health
Health Management Appeals Department
P.O. Box 3264
Milwaukee, WI 53201-3264

Telephone: 800-454-5105, ext. 6239
Fax: 414-299-7555, Attention: Health Management Appeals Department

Level II Appeal Request

If you wish to appeal the Level I Appeal decision, you or your designated representative may request a Level II Appeal Panel review. This request must be received in writing at the above address within sixty (60) days of the date of the Level I Appeal decision letter.

- Include in your request any additional medical information that you feel is pertinent to your case.
- We will send you written acknowledgement of your request.
- You shall have the opportunity to appear before the Appeal Panel.
- The Level II Appeal Panel review will be completed within thirty (30) calendar days of the receipt of your request. We will notify you in writing of the decision.

If you have not yet received the services you are appealing:

For pre-service appeals, all of the steps outlined above under Level I and Level II will be combined into one final appeal process and will be completed within 30 calendar days of receipt of the appeal request. "Pre-Service" means any claim for a benefit under a group health

plan with respect to which the terms of the plan condition receipt of the benefit, in whole or in part, on approval of the benefit in advance of obtaining medical care.

Our internal appeals process will be exhausted upon completion of the pre-service appeal or the Level II Appeal Panel decision. If your coverage with us is through an employee benefit plan that is established or maintained by an employer or employee organization, after exhausting the internal appeal processes, you have the right to bring a civil action under ERISA section 502(a).

If your coverage with us is through an employee benefit plan that is established or maintained by an employer or employee organization, you may have reasonable access to all documents, records and other information relevant to your claim or request for benefits and obtain a copy of such information free of charge, upon request.

Independent External Review

If you are dissatisfied with the Level II Appeal Panel decision, you may have the right to file a request for an independent external review. You may apply for an independent external review directly with us at the above listed address after all internal appeals processes have been exhausted. In order to qualify for this review, the final adverse decision by Assurant Health must concern whether a course or plan of treatment is medically necessary, experimental or investigational, or an active course of treatment for purposes of obtaining continuity of care under Oregon law. You must request an external review not later than the 180th day after receipt of Assurant Health's final written decision. The request must include a signed waiver granting the independent external review organization access to your medical records.

Within 2 business days of receiving your request, we will send the request to the Oregon Insurance Division, which will assign an independent review organization (IRO).

The IRO will review the dispute and issue a written decision. An IRO has 30 days to issue a decision after you apply to the insurer for an external review.

You may qualify for an expedited external review if a provider with an established clinical relationship to you certifies in writing and provides supporting documentation that the ordinary time period for external review would seriously jeopardize your life or health or your ability to regain maximum function. Also, you qualify for an expedited external review if your request is regarding mastectomy-related services. In this case, we will inform the Insurance Division that the referral is expedited. If you qualify for an expedited review, a decision shall be issued by the IRO within three days of the request.

Assurant Health is not bound by the decisions of independent review organizations. Assurant Health may follow nonetheless a decision by an independent review organization. If we do not comply with the decision, you have a right to sue us.

You have the right to file a complaint or seek other assistance from the Oregon Insurance
Division.

Assistance is available:

Group v.2
E/I

By calling 503- 947-7984;

By writing to the Oregon Insurance Division
Consumer Protection Unit
350 Winter St. NE, Rm 440-2
Salem, Oregon 97301-3883
Fax 503- 378-4351
888- 877-4894 (toll-free message phone)
E-mail address: dcbs.insmail@state.or.us;

Through the internet at <http://www.cbs.state.or.us/external/ins/>